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Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment

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ABSTRACT Malignant pleural mesothelioma is an aggressive malignancy of the pleural surface, predominantly caused by prior asbestos exposure. There is a global epidemic of malignant pleural mesothelioma underway, and incidence rates are predicted to peak in the next few years.

This article summarises the epidemiology and pathogenesis of malignant pleural mesothelioma, before describing some key factors in the patient experience and outlining common symptoms. Diagnostic approaches are reviewed, including imaging techniques and the role of various biomarkers. Treatment options are summarised, including the importance of palliative care and methods of controlling pleural effusions. The evidence for chemotherapy, radiotherapy and surgery is reviewed, both in the palliative setting and in the context of trimodality treatment. An algorithm for managing malignant pleural effusion in malignant pleural mesothelioma patients is presented. Finally new treatment developments and novel therapeutic approaches are summarised.



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This article on mesothelioma describes pathogenesis, symptoms, diagnostic approaches and treatment options <http://ow.ly/cjkb305aQGz>

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive cancer of the pleural surface. It is associated with previous asbestos exposure, with a latency period of ~40 years between fibre exposure and disease presentation [1–5].

Global incidence of MPM has risen steadily over the past decade, and is predicted to continue to an estimated peak in 2020 [1, 2]. Precise numbers are difficult to determine as the disease is likely to be under reported in areas of low incidence. However, an estimate based on 2008 data suggested an average of 14 200 cases worldwide each year [6]. Total incidence is highest in the USA and UK although per capita, Australia and Italy also rank highly. Unfortunately the ongoing, unregulated use of asbestos in industrial countries such as India, Brazil and Russia means that MPM will continue to represent a significant global health concern even after peak incidence has passed.

Prognosis with MPM is poor and median survival ranges from 8 to 14 months from diagnosis [1–3, 7]. Women have a more favourable outlook than men, but due to the occupational nature of the disease there is a male predominance of 4:1 [7]. There are four main histological sub-types; epithelioid, sarcomatoid, biphasic or mixed, and desmoplastic. The sarcomatoid variant is associated with the worst outcomes, with a median survival of just 4 months. In contrast, epithelioid has the most favourable prognosis with a median survival of 13.1 months [1, 2, 7].

This article will summarise the pathogenesis of MPM, before describing symptoms and exploring elements of the patient's experience. Diagnostic approaches, including biomarkers and radiological imaging will be outlined. The evidence for chemotherapy, radiotherapy and surgery will be reviewed and new directions for the future will be presented.

Pathogenesis

The majority of MPM cases are caused by prior exposure to asbestos, often occurring >40 years previously [1–5]. Asbestos is a naturally occurring silicate mineral that has two different structural forms: the curly, serpentine fibres of chrysotile or “white” asbestos and the sharp, needle-like fibres of amphibole asbestos. The latter can be further divided into crocidolite (blue) asbestos, amosite (brown) asbestos, and anthophyllite, actinolite and tremolite. The risk of developing MPM is related to the type of fibre, as well as to the heaviness and duration of exposure [1].

MPM is classified as an occupational disease since asbestos exposure occurs mainly in the workplace. However, para-occupational exposure can occur, for instance in wives of asbestos workers who launder their clothes [1, 4]. Additionally, asbestos exposure may have occurred outside the workplace or could have happened unbeknownst to the patient.

Other causes of MPM include erionite (a mineral found in the rocks of Turkey), chest wall radiation and simian virus 40. The latter, an oncogenic virus that blocks tumour suppressor genes, may act as a cofactor in the development of MPM, although the evidence for causality is weak [1, 5, 8–12].

The mechanism of carcinogenesis in MPM is multifactorial. Asbestos fibres are inhaled and migrate to the pleura. Within the pleural space, fibres cause irritation and a repeated cycle of tissue damage and repair is established. The presence of oxygen free radicals, released by asbestos fibres when phagocytosed by macrophages, causes intra-cellular DNA damage and abnormal repair [5]. Asbestos fibres also penetrate mesothelial cells, where they interfere with mitosis, generate mutations in DNA and alter chromosome structure. Asbestos-exposed mesothelial cells release inflammatory cytokines, including tumour growth factor- β , platelet-derived growth factor and vascular endothelial growth factor (VEGF) [5]. This creates a favourable microenvironment for tumour growth. Finally, asbestos induces the phosphorylation of various protein kinases (mitogen-activated protein and extracellular signal-regulated kinases 1 and 2), leading to increased expression of proto-oncogenes and further promotion of abnormal cellular proliferation [13].

Genetic profiling of MPM tumours has unveiled common mutations, including reduced expression of key molecules in the p53 tumour-suppressor gene pathway, such as p14, p16 and NF2-MERLIN [13]. Deletions and loss mutations of other genes, including BRCA-associated protein 1 (BAP1), set domain containing 2 (SETD2), DDX3X, unc-like autophagy activating kinase (ULK2), ryanodine receptor 2 (RR2), cilia and flagella associated protein 45 (CFAP45), set domain bifurcated 1 (SETDB1) and DDX51, have also been demonstrated in MPM [14]. However, compared to many tumours, MPM has a low frequency of protein-altering mutations (~25 mutations per tumour) [15]. This limits the potential for molecular targeted therapy as oncogene-addiction is less likely to occur in MPM [16].

The patient's perspective

Informing someone that they have MPM is, whilst necessary, often devastating for the patient. They face a barrage of bad news relating to the incurable nature of MPM, its poor prognosis and the limited treatment options.

As a result, many patients are left with feelings of hopelessness and uncertainty about the future [17–19]. Depression and anxiety are common and found more frequently in MPM compared with other tumours [17, 20–22].

The classification of MPM as an industrial injury generates complex compensation and benefits claims, which can be time-consuming and stressful [18, 22]. Legal requirements after death, such as coroner's inquests and potentially a *post mortem*, create an additional burden for family members [18, 19, 22, 23]. The occupational nature of MPM can create feelings of anger towards previous employers or concern for family members and colleagues who may have been similarly exposed [24]. Some patients will have seen colleagues die of MPM and describe a sense of anticipatory anxiety, known as the “Damocles syndrome”, created by the knowledge that they are similarly at risk [22, 24].

Therefore, accurate and sensitively delivered information is crucial. In the UK mesothelioma specialist nurses are a valuable resource in this regard. They act as key workers, offering practical and emotional support, and providing a consistent presence at clinic appointments. Their presence can reduce patients' experience of care as “fragmented” and ameliorate anxiety by providing continuity and consistency [23]. In centres where specialist nurses are not available, all team members should collaborate to ensure they are providing integrated care for the complex needs of individual patients.

Symptoms

The majority of patients with MPM present with breathlessness, chest pain or both [1, 2, 18, 25–30].

In the early stages of disease breathlessness is usually due to a pleural effusion, found in 70% of patients at presentation [25]. However, as the disease progresses, pleural effusions tend to diminish, either as a result of medical intervention or obliteration of the pleural space by the tumour [25]. As the disease extends around the pleural surface, breathlessness occurs as a result of restricted respiratory movement and encasement of the lung by the tumour [1, 25].

Chest pain is common and can be caused by the effusion or the tumour. It is usually dull and heavy and sometimes described as a “dragging” sensation [1, 31]. Pleuritic pain is less common, but can occur in the presence of parietal pleural irritation [1, 2, 27]. Chest pain tends to worsen as the disease progresses, particularly if invasion of the chest wall occurs [32]. Bone pain secondary to rib invasion or neuropathic pain from intercostal nerve involvement may also feature [31, 32].

Other symptoms of MPM include fatigue, anorexia, weight loss, sweats and malaise [1, 2, 18, 25–29, 31]. These are a result of circulating cytokines, released by both the tumour and host in response [33]. Cough, haemoptysis and lymphadenopathy are less common in MPM compared with bronchogenic tumours [1]. However, local tumour invasion can cause superior vena cava obstruction, laryngeal nerve palsy or dysphagia [1, 2, 25]. The latter is often a pre-terminal event [1].

Some patients are asymptomatic, and have an abnormality detected on imaging undertaken for a different reason [1]. Asymptomatic patients appear to have longer survival, probably because they are diagnosed earlier in the disease process [34]. For this reason it is important to carefully monitor patients who present with a pleural effusion with a background of previous asbestos exposure, even if the effusion is small or resolves spontaneously. A proportion of these patients will develop MPM in the future, and active follow-up increases the chance of making the diagnosis early in these people [35].

Diagnosis

MPM is a challenging diagnosis to make. Radiological imaging should be undertaken in all patients as it can provide valuable diagnostic and staging information. The advantages and limitations of the different imaging modalities are outlined below.

Biomarkers are useful diagnostic and prognostic tools in other cancers [36, 37]. In MPM a number of different biomarker tests have been evaluated. However, to date, MPM biomarkers have been found to be imperfect and of limited clinical use. The evidence is summarised below.

Further investigation of suspected MPM requires sampling of pleural fluid for biochemical and cytological examination. Unfortunately, cytological yield is low in MPM, and biopsies are usually required to confirm the diagnosis and identify the histological sub-type [1, 35, 38]. Biopsies can be obtained percutaneously under radiological guidance, or under direct vision at thoracoscopy, either as a local anaesthetic procedure (medical thoracoscopy) or as a surgical intervention (video-assisted thoracoscopic surgery (VATS)) [39]. The choice of biopsy technique will vary between patients depending on the distribution and morphology of their disease, their suitability for surgery or invasive procedures and the availability of services [39]. The evidence for the various biopsy approaches has been discussed elsewhere and is not included in this article [39].

Staging

Staging MPM is difficult due to limitations in current imaging techniques, specifically in the accurate assessment of tumour size and nodal involvement [2]. Surgical thoracoscopy, with additional mediastinoscopy to assess suspected nodal disease, is superior to computed tomography (CT) and is the current gold standard for staging in MPM [40]. However, not all patients are suitable to undergo this procedure, and therefore image-based staging, whilst imperfect, is employed for many MPM cases.

There are a number of staging classifications for MPM, all of which have limitations for use in routine clinical practice [2]. The consensus is that a tumour, node, metastasis-based system, using surgical information where available and radiology in its absence, should be employed to determine prognostic outlook in all patients with MPM. One such system is the International Mesothelioma Interest Group staging classification (table 1) [41].

Imaging

Imaging plays a major role in the assessment of patients with suspected MPM, and can contribute both diagnostic and staging information. However, radiological interpretation can be difficult if pleural thickening is minimal or absent, and staging is often challenging due to the heterogeneous growth pattern of the tumour.

Chest radiography is usually the first investigation performed. Typical findings include a pleural effusion, loss of hemithoracic volume, nodular pleural thickening, irregular fissural thickening or a localised mass lesion. The presence of pleural plaques may alert the clinician to prior asbestos exposure, even in the absence of known exposure. However, chest radiograph appearances are generally insensitive and nonspecific and further imaging is usually required [42].

Bedside thoracic ultrasound is commonly performed by respiratory physicians to assess pleural fluid volume, distribution and echogenicity, and to determine a safe site for aspiration [43]. Thoracic ultrasound allows visualisation of pleural fluid, pleural thickening and any tumours or nodularity on the pleura or hemidiaphragm (figure 1). Sonographic features that suggest pleural malignancy include pleural-based mass lesions, pleural thickening >1 cm, nodular pleural thickening and diaphragmatic nodularity [44]. These features have a specificity of >95% with regard to malignancy [44]. However, sensitivity is low at 40%, and consequently patients with nonspecific thoracic ultrasound findings require further investigation if MPM is suspected.

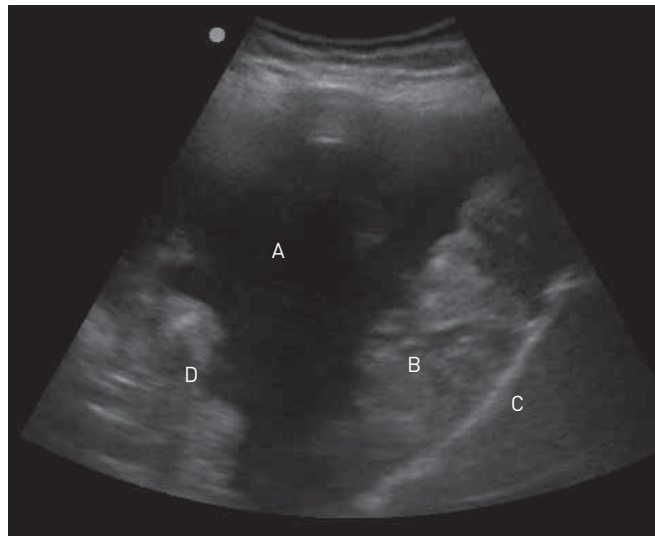
CT imaging is vital in patients with MPM. CT features of pleural malignancy include pleural enhancement, infiltration of the chest wall, mediastinum or diaphragm, nodular or mediastinal pleural thickening and interlobar fissural nodularity [45]. Some studies have reported high sensitivity and specificity associated with these features; however, appearances can be subjective and are highly operator dependent. A recent review of the “real-life” diagnostic performance of CT reported a sensitivity and specificity of 68% and 78%, respectively, for pleural malignancy [46]. CT cannot reliably differentiate MPM from metastatic pleural malignancy, although circumferential pleural thickening and mediastinal pleural involvement are more

TABLE 1 The International Mesothelioma Interest Group Staging System for malignant pleural mesothelioma

T	
T1	Tumour of the ipsilateral parietal pleura, including diaphragm and mediastinal pleura
T1a	No visceral pleural involvement
T1b	With visceral pleural involvement
T2	Tumour affecting parietal, visceral, diaphragmatic and mediastinal pleura, with either involvement of diaphragmatic muscles or pulmonary parenchyma
T3	Involvement of the endothoracic fascia, extension into the mediastinal fat, non-transmural involvement of the pericardium or resectable focus of chest wall invasion
T4	Unresectable disease, diffuse chest wall or mediastinal involvement, direct transdiaphragmatic spread into the peritoneum, contralateral pleural involvement, invasion of the spine, ribs or brachial plexus, trans-mural pericardial invasion or malignant pericardial effusion
N	
N0	No regional lymph node metastases
N1	Metastases in ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in subcarinal or ipsilateral mediastinal lymph nodes, including ipsilateral internal mammary chain
N3	Contralateral lymph node metastases, ipsilateral or contralateral supraclavicular lymph node involvement, and scalene nodes
M	
M0	No extrathoracic metastases
M1	Extrathoracic metastases present

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FIGURE 1 Ultrasound demonstrating large echoic effusion (A) above a flattened diaphragm (B) with extensive thick, irregular nodularity arising from the diaphragm (C) and visceral pleural (D). This is highly suspicious for malignancy, most likely malignant pleural mesothelioma.



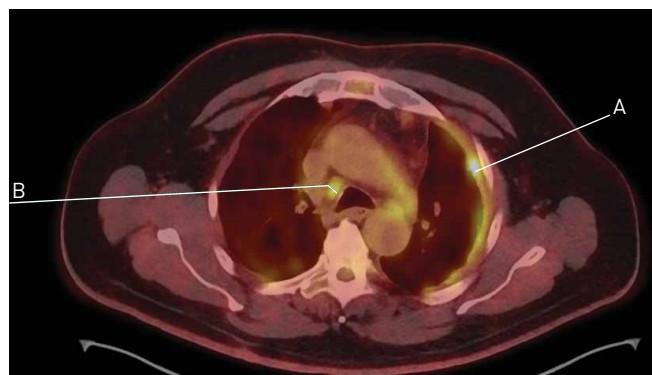
frequent in MPM [47]. Similarly CT cannot reliably distinguish between MPM subtypes, although ipsilateral volume loss, interlobar fissural involvement and mediastinal pleural involvement are reported more frequently in sarcomatoid disease [48, 49].

CT staging is useful in MPM, as advanced stage disease is associated with worse prognoses [50]. However, accurate staging can be challenging as identification of nodal metastases is difficult on CT and subtle chest wall or diaphragm invasion may be missed [40]. Further imaging with positron-emission technology (PET)-CT or magnetic resonance imaging (MRI) can provide additional information in this regard.

PET-CT combines high-resolution CT scanning with an injection of a radioactive metabolic tracer (*e.g.* 18-fluoro-deoxy-glucose (FDG)) which accumulates at areas of metabolic activity (figure 2). FDG uptake is assessed at regions of interest and reported as standardised uptake values (SUV). Maximum SUV is higher in MPM than benign disease, and a threshold value of 2 can reliably differentiate between benign and malignant disease [51, 52]. However, PET-CT cannot identify MPM from metastatic pleural malignancy, and there does not appear to be any correlation between maximum SUV and histological sub-type [51]. Because FDG uptake is a marker of metabolic activity, false negatives are possible in early disease or in tumours with a low proliferation rate. Conversely, inflammatory disorders such as rheumatoid pleuritis and tuberculous pleurisy can produce false-positive results, as can prior pleurodesis [53]. Consequently, sensitivity and specificity are not high enough to support the use of PET-CT in routine diagnostic practice, although it may have a role in identifying suitable targets for biopsy [54]. PET-CT is also able to identify malignant nodal disease and extrathoracic metastases with greater accuracy than CT or MRI and may have a role in staging, particularly in patients undergoing surgery [55, 56].

Unfortunately, PET-CT suffers from poor spatial resolution, which results in low sensitivity for extrapleural invasion. MRI is superior in this regard with excellent spatial and contrast resolution. In a prospective series of 69 patients being considered for surgical resection, contrast-enhanced MRI detected the presence of chest wall, mediastinal or diaphragmatic involvement in 17 (22%) patients in whom CT had not demonstrated invasive disease [57]. The sensitivity for detecting T3 disease with MRI was 85%,

FIGURE 2 FDG (18-fluoro-deoxy-glucose)-positron emission tomography showing malignant pleural mesothelioma. A: an area of high FDG uptake (maximum standardised uptake value of 13.4) in the left lateral pleura beneath the third rib. B: a right paratracheal lymph node with maximum standardised uptake value of 4.6.



with 100% specificity. Consequently MRI is useful in assessing for infiltrative disease that would preclude surgical resection.

As well as identifying morphological features of malignancy, MRI can provide functional information *via* the use of contrast agents, *e.g.* gadolinium, or methods such as diffusion-weighted imaging-MRI or dynamic contrast enhancement-MRI. Combining functional data with standard imaging produces sensitivity and specificity rates >90% for differentiating malignant pleural disease from benign [45, 58, 59]. Despite this, MRI is not routinely used for diagnostic purposes in MPM.

Biomarkers

A reliable diagnostic biomarker that offers high diagnostic sensitivity and specificity would be a major advancement for MPM. However, despite promising early results no such biomarker has been identified. Studies have been disadvantaged by retrospective designs, use of selected MPM cohorts, inappropriate controls and inconsistent sampling protocols, assay methods and cut-off points. The most widely studied and promising markers are summarised below.

Mesothelin is a cell-adhesion glycoprotein that is over-expressed in MPM [60, 61]. Serum mesothelin (or serum mesothelin-related protein) levels are elevated in patients with MPM in comparison to asbestos-exposed controls [62, 63]. The diagnostic value of mesothelin appears to be highest in patients with advanced stage epithelioid tumours [64]. It is less useful in sarcomatoid sub-types as these tumours rarely express mesothelin. A meta-analysis of data from 4491 individuals, of whom 1026 had MPM, reported a sensitivity of 32% for serum mesothelin with 95% specificity [64]. This is insufficient for diagnostic purposes [38]. Pleural fluid mesothelin levels share similar diagnostic performance rates to serum, with a meta-analysis of 11 studies calculating an overall sensitivity and specificity of <60% and 90%, respectively [65]. Consequently, a high serum or pleural fluid mesothelin level should prompt further investigations for malignancy, but a negative test is of limited value.

Other blood-based biomarkers that have been explored in MPM include megakaryocyte potentiating factor (an alternative cleavage product of the mesothelin precursor protein) and the glycoproteins osteopontin and fibulin 3. Studies of these biomarkers suffered from methodological problems including inconsistent diagnostic cut-off levels and lack of external validation [62, 66–68]. However, none of these biomarkers have demonstrated diagnostic superiority over mesothelin and consequently they have no role in clinical care at present. Fibulin 3 is also found in pleural fluid, and high levels appear to correlate with advanced disease [67]. Its diagnostic ability is limited, but it may be of value as a prognostic tool [66, 67].

Recently, a proteomics-based biomarker detection technique has been developed in the form of SOMAscan (SomaLogic Inc., Boulder, CO, USA). This 13-protein classifier differentiated MPM from controls with a sensitivity and specificity of 93% and 91%, respectively, but external validation is required [69]. Interestingly, the 13 proteins used in this technology have not previously been associated with MPM and their identification may provide potential targets for novel drugs or diagnostic strategies.

Management

There is no curative treatment for MPM. Systemic treatment options include chemotherapy, targeted therapy and radiotherapy, delivered separately or as part of multimodality treatment. Surgery is controversial and limited to patients with early stage disease and good functional status. Palliative care and symptom management are essential and the control of pleural effusions is an important factor. A number of novel therapeutic agents are under investigation, and may provide further treatment options for MPM in the future.

MPM patients should be discussed at a specialist mesothelioma multidisciplinary team meeting, as recommended in the 2007 UK Department of Health's Mesothelioma Service Framework and the British Thoracic Society's Statement on Mesothelioma [1, 70]. Discussion at a specialist multidisciplinary team provides expert advice on investigation and management, as well as additional benefits such the opportunity to participate in clinical trials [70, 71].

Chemotherapy

Chemotherapy is the only treatment modality that has been shown to improve survival in MPM. However, prior to 2003 the evidence was poor and based on underpowered, early phase trials [72]. Response rates were low and survival was universally <10 months [73]. One large randomised trial demonstrated that the addition of chemotherapy to active symptom control offered no survival benefit and no improvement in quality of life compared with active symptom control alone [28].

However, in 2003 two pivotal phase III trials were published that changed the landscape of chemotherapy in MPM [74, 75]. The trials used third-generation anti-folate agents aimed at inhibiting DNA synthesis and preventing tumour proliferation. The first trial randomised 448 treatment-naïve participants to receive

either pemetrexed and cisplatin or cisplatin alone [74]. Median survival in the pemetrexed arm was 12.1 months, compared with 9.3 months with cisplatin alone ($p=0.02$). Toxicity rates were high initially, but fell after the addition of vitamin B12 and folic acid supplementation. On the basis of this trial, pemetrexed was approved by global marketing authorities for use in combination with cisplatin for MPM. Over 10 years later, it remains the standard first-line chemotherapy for patients with MPM.

The second trial compared raltitrexed and cisplatin with cisplatin alone in 250 participants [75]. Survival benefit was similar to that seen in the pemetrexed trial (11.4 months *versus* 8.8 months, $p=0.048$) although objective response rates were lower [74, 75]. The study appeared underpowered, and consequently had less impact on clinical care. At present raltitrexed is not licenced by the US Food and Drug Administration or the European Medicines Agency for use in MPM.

Carboplatin can be substituted for cisplatin in older patients, patients with comorbidities or patients who experience toxicity with cisplatin, as it is generally better tolerated. In a meta-analysis, carboplatin demonstrated similar efficacy to cisplatin, and phase II trials have shown enhanced overall survival and longer progression-free survival (PFS) in patients with MPM treated with carboplatin and pemetrexed [76–79].

An important issue in MPM chemotherapy is predicting which patients will respond to treatment. An evaluation of over 1700 patients who received pemetrexed with either cisplatin or carboplatin as part of an expanded access programme demonstrated response rates of 26.3% and 21.7%, respectively [80]. These low response rates, combined with a lack of reliable biomarker to identify potential responders, are likely to be responsible for the low uptake of chemotherapy in some centres [7].

There are many unanswered questions regarding chemotherapy and MPM. It is not known whether immediate chemotherapy is more effective than chemotherapy delayed until the appearance of symptoms. A small pilot study suggested a trend for slower progression and longer survival with early chemotherapy, but larger trials are needed [29]. Similarly, the optimum number of cycles of chemotherapy and the role of maintenance pemetrexed are unclear. In nonsmall cell lung cancer, four cycles of chemotherapy has similar efficacy to six cycles, but with lower toxicity [81]. Could the same be true for MPM? Alternately, is there any benefit from continuing pemetrexed as maintenance therapy following an initial response? Maintenance pemetrexed is safe and well-tolerated, but randomised efficacy data is awaited [82]. Finally the best second-line agent is unknown. Phase II trials support the use of vinorelbine, or gemcitabine/cisplatin doublet, but re-treatment with pemetrexed may also be effective in previous responders [83–87].

Targeted therapy

VEGF plays a key role in MPM by promoting angiogenesis and stimulating tumour growth [5, 88]. Recently, bevacizumab, an anti-VEGF monoclonal antibody, has been shown to be effective in MPM [89]. The multicentre, phase III MAPS trial randomised 448 participants with MPM to receive cisplatin and pemetrexed chemotherapy with or without bevacizumab. Patients who received bevacizumab had significantly longer median (95% CI) overall survival at 18.8 (15.9–22.6) months compared with 16.1 (14.0–17.9) months in the chemotherapy alone arm ($p=0.017$). Patients given bevacizumab alongside chemotherapy also showed longer PFS of 9.2 (8.5–10.5) months *versus* 7.3 (6.7–8.0) months in those receiving standard care ($p<0.0001$) [89]. This difference was seen despite a higher proportion of patients stopping bevacizumab early, and a greater number of post-study treatments given to the control group. Adverse event rates were similar between groups, although thromboembolic complications and kidney impairment were more common with bevacizumab. The authors conclude that the use of bevacizumab is warranted alongside first-line standard chemotherapy in patients with unresectable MPM [89]; an opinion that is supported by an editorial in the same journal [90].

Radiotherapy

Radiotherapy is used in two main settings in MPM: as a palliative measure to treat symptoms or an adjuvant to surgery and chemotherapy in the context of trimodality treatment. Evidence for the latter technique is limited to anecdotal reports in highly selected patients, and as a result trimodality treatment is not considered standard care for MPM. The literature relating to trimodality treatment is reviewed in a later section.

Radiation is administered using the highly precise intensity-modulated radiotherapy technique as the alternative, high-dose external-beam hemithoracic radiotherapy, was associated with significant toxicity. Intensity-modulated radiotherapy technique allows accurate three-dimensional mapping of the tumour, thus reducing the likelihood of radiation injury to surrounding organs [91]. Nonetheless, toxicity remains a risk, with eight (30%) out of 27 patients experiencing radiation pneumonitis in a recent phase II study [91].

In the palliative setting, radiotherapy can reduce tumour bulk and relieve symptoms, particularly in the context of chest wall invasion, nerve root involvement or painful cutaneous metastases. The prospective phase II SYSTEMS trial showed that a dose of 20 Gy, delivered in five daily fractions, reduced

patient-reported pain scores by $\geq 30\%$ in 14 (35%) out of 40 participants [92]. Further trials evaluating the optimum radiotherapy dose and choice of regimen are underway.

Radiotherapy has been used prophylactically to prevent sub-cutaneous metastases developing due to tumour seeding along procedure tracts. One small randomised trial using three daily fractions of 7 Gy after thoracoscopy resulted in no tract metastases in the treatment group compared with eight (40%) out of 20 patients in the control arm [93]. However, this result has never been replicated, and subsequent randomised trials reported no difference in tract metastases following prophylactic radiotherapy [94, 95]. The only suitably powered, randomised trial to date reported no difference in the frequency of tract metastases in patients receiving immediate radiotherapy after large-bore chest interventions compared with those receiving it when required. Consequently, the use of prophylactic radiotherapy is likely to diminish.

Surgery

The benefit of surgery in MPM is much debated, and there is a need for robust randomised trial data to elucidate its efficacy and clarify its role in management [1, 96, 97].

There are two approaches to surgery in MPM: radical removal of all visible disease or a more conservative, tissue-sparing, debulking procedure. The more radical option is extrapleural pneumonectomy (EPP), an operation which aims to eradicate all macroscopic tumour *via* the removal of lung, pleura, pericardium and diaphragm [98]. The original descriptions of EPP reported enhanced survival, but mortality and complication rates were high [98–101]. Additionally, these reports were based on retrospective data from highly selected patients, with no control arm and no information about the population from which they were drawn. Consequently, a systematic review concluded that it was impossible to determine whether EPP extended survival in people with MPM [102].

The only randomised trial to assess EPP in MPM was the Mesothelioma and Radical Surgery trial (MARS), a feasibility study whose primary aim was to determine whether a full-scale trial would be possible [103]. The trial experienced practical issues, including lengthy recruitment and non-compliance with randomisation (six out of 26 participants allocated to “no EPP” sought and received surgery off-trial). Analysis of clinical outcome data revealed potential harm associated with EPP with an adjusted hazard ratio for death of 2.75 (95% CI 1.21–6.26; $p=0.016$). As a result of this, and observational studies suggesting similarly poor outcomes, EPP has been largely abandoned in favour of less radical procedures [104–107].

Extended pleurectomy with decortication (also known as pleurectomy and decortication or pleurectomy/decortication) is a lung-sparing procedure in which the visceral and parietal pleura are removed. It is associated with fewer surgical complications than EPP, and potentially better survival [105, 107–109]. PD is a “de-bulking” procedure, and unlike EPP does not aim for macroscopic complete resection. Consequently it is often employed alongside multi-modality treatment [109–113]. To date, there is no randomised data focussing on whether PD extends survival compared with no surgery; however, the multicentre MARS-2 trial is currently underway and aiming to answer this question [114].

Another non-radical approach is partial pleurectomy *via* VATS. Non-randomised studies suggested that VATS-partial pleurectomy controlled symptoms in MPM, and possibly improved survival [115, 116]. However, the only suitably powered randomised trial to examine this demonstrated no survival difference compared with talc pleurodesis *via* a chest drain [117]. VATS-partial pleurectomy had higher rates of pleurodesis in the first 12 months, but at the expense of a greater number of surgical complications and a longer hospital stay. Consequently VATS-partial pleurectomy cannot be recommended for MPM, and non-surgical pleurodesis methods should be employed to control pleural fluid.

Trimodality treatment

Trimodality treatment for MPM consists of induction chemotherapy followed by EPP with subsequent hemithoracic radiotherapy. Non-randomised studies in carefully selected patients reported median survival times of up to 29 months and a systematic review concluded that trimodality treatment may be beneficial for certain patients [118–120]. However, a subsequent large randomised trial reported no difference in PFS or overall survival in patients treated with neoadjuvant chemotherapy and EPP with or without radiotherapy [121]. There were 12 adverse events of grade 3 or higher in 27 patients treated with radiotherapy, including one death from radiation pneumonitis. The study concluded that the addition of hemithoracic radiotherapy to EPP and chemotherapy added an unnecessary burden without offering benefit.

An alternative approach involves delivering high-dose radiotherapy prior to EPP, followed by adjuvant chemotherapy if there is lymph node involvement at surgery. This approach, nick-named SMART (Surgery for Mesothelioma After Radiation Therapy), was shown to be feasible in an initial series of 25 patients and appeared to be particularly efficacious in patients with epithelioid sub-type tumours [122].

Updated results for 62 patients treated with SMART showed a median survival of 36 months, with greatest benefit again seen in patients with epithelioid tumours [123]. However, it must be noted that these reports represent highly selected patients, operated on in a single centre with extensive MPM expertise and the results may not be generalisable. At present trimodality treatment is not recommended in the standard care pathway for MPM.

Management of malignant pleural effusions

The majority of patients with MPM experience a pleural effusion at some point. Drainage of pleural fluid improves breathlessness and prevention of fluid re-accumulation can improve quality of life long term [124]. There are a number of methods for achieving pleural fluid control, each with benefits and disadvantages. A flowchart to help decide which procedure is best for an individual patient is shown in figure 3.

Therapeutic pleural aspiration is the simplest approach, and most patients will undergo this intervention at least once in their disease pathway. However, fluid inevitably re-accumulates and further interventions are required [30, 72]. Repeated aspirations may be appropriate for patients with a very short life expectancy, but a definitive procedure is generally preferable [2, 30, 72].

Definitive fluid control can be achieved with chemical pleurodesis, a procedure aiming to obliterate the pleural space and render fluid re-accumulation impossible. For successful pleurodesis to occur there must be direct apposition of enough healthy pleural tissue to allow pleural inflammation and adhesion to occur when a chemical irritant is instilled into the pleural space. Consequently patients with trapped lung or extensive tumour bulk should be considered for alternative methods of pleural fluid control.

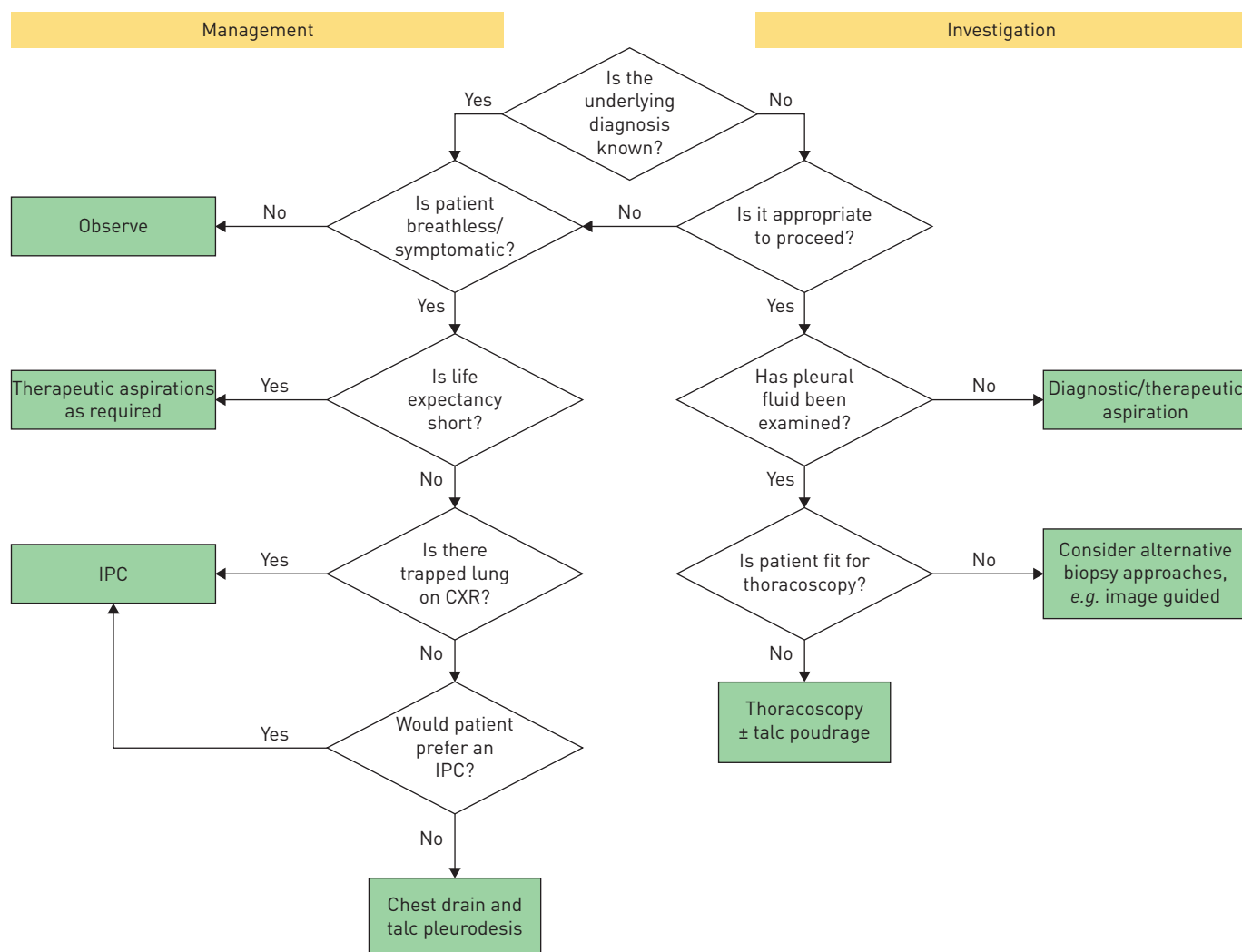


FIGURE 3 Flowchart demonstrating the decision making process for investigating and managing pleural effusions in malignant pleural mesothelioma. IPC: indwelling pleural catheter; CXR: chest radiograph.

Many chemical agents have been used for pleurodesis, but sterile, medical-grade talc appears to be the safest and most effective [125–129]. The British Thoracic Society recommends talc as the pleurodesis agent of choice, although other agents such as bleomycin and tetracycline are used in other countries [30, 130].

Talc can be delivered into the pleural space as thoracoscopic poudrage (figure 4) or as slurry *via* a chest drain. Talc pleurodesis is successful in 60–80% of people provided the underlying lung is not trapped [30, 124, 131]. There is weak evidence suggesting poudrage may be more effective than slurry, but access to thoracoscopy is not universal and some patients may not be suitable for this more invasive procedure [132–134]. For those that are, thoracoscopy has the additional benefit of allowing patients to obtain a diagnosis and undergo pleurodesis in one sitting [39].

An alternative to pleurodesis is the placement of an indwelling pleural catheter. This allows regular home drainage, and provides long-term relief of breathlessness [124]. Indwelling pleural catheters are as effective at relieving symptoms as talc slurry *via* a chest drain, and have the additional benefit of being appropriate for patients with trapped lung [124]. In situations where both indwelling pleural catheters and talc pleurodesis are available, management should be led by patient choice [135].

Palliative care

The British Thoracic Society, the European Respiratory Society and the International Mesothelioma Interest Group all emphasise the importance of good palliative care to help manage physical symptoms and offer psychological, emotional or spiritual support [1, 2]. Given the lack of curative treatment and the limited life expectancy, the overriding aim with MPM is to maintain quality of life and allow patients to live a meaningful and dignified life [1]. A multicentre randomised controlled trial is currently underway evaluating whether early specialist palliative care involvement improves patient-reported quality of life in MPM [136].

Future therapies

Numerous novel agents have been investigated in MPM. Amongst those that have demonstrated efficacy are targeted therapies to epidermal growth factor receptor antagonists and platelet-derived growth factor receptor inhibitors. However, more accurate tumour profiling and identification of biomarkers are needed in order to identify the patients most likely to respond [137–140].

Immunotherapy has shown promise in MPM. Checkpoint inhibitors such as tremelimumab and pembrolizumab have shown impressive disease control rates and prolonged disease stability when used as first-, second- or third-line treatment [141–145]. The combination of chemotherapy with immunotherapy, or multiple immunotherapy agents, appears synergistic in other tumours and warrants further exploration in MPM [146–148]. Numerous trials are currently underway exploring alternate immunotherapy agents and combinations (www.clinicaltrials.gov).

Mesothelin-targeted treatments are another area of interest in MPM. Agents that have undergone early phase clinical trials include mesothelin-specific monoclonal antibodies (*e.g.* amatuximab), anti-mesothelin immunotoxins (*e.g.* SS1P), mesothelin tumour vaccine (CRS-207) and chimeric antigen receptor T-cells targeted to mesothelin [149–153]. Phase II and III trials are underway.



FIGURE 4 Talc poudrage seen at thoracoscopy. A: parietal pleura with ribs visible beneath and a fine layer of talc covering most of its surface. B: malignant-looking nodule on the parietal pleura. C: collapsed lung with talc covering its surface. D: talc collecting in the para-spinal gutter.

Finally intra-pleural gene therapy using an adenovirus vector has been shown to be safe and feasible in MPM, with promising median survival in a pilot study of 40 patients [154]. A multicentre randomised trial is planned.

Overall, the future of MPM looks likely to contain many more therapeutic options than are currently available. Personalised treatment based on individual patient characteristics and tumour genetics is distinctly possible. Combination therapy is likely to generate a significant breakthrough in the next few years.

Conclusion

MPM is a complex disease that causes significant morbidity and mortality. Diagnostic difficulties complicate matters, although there is potential for developments in the field of imaging and biomarkers in the next few years. Treatment options remain limited, but the recent trial supporting the use of the targeted therapy bevacizumab has given hope that this may be changing. Many new treatments are under investigation and it is likely that the future of MPM will involve highly individual, personalised treatment.

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